Introduction to Heme/Onc

Introduction

Hematology is actually really simple—in retrospect. It is not easy to get started if you have a limited foundation. This lesson assumes you know less than you probably know, explaining what blood is, going over the layout for the Hematology module, and discussing the different blood products and their indications. We try to give you the clinical perspective, introducing the "CBC sticks" (the shorthand way of writing down a CBC on a data tracker) and using it as the springboard for discussion. If you start this lesson and feel you are beyond it, check out the first lesson of either the Anemia or Clotting series. If you're comfortable, you can probably skip the General series. But those later series are going to assume you know everything in General, and will not slow down for you to catch up.

What Blood Is

Whole blood, the thing we draw out of a person's vein, is separated into three main categories, taken from what happens when we put blood into a centrifuge and spin that sample down: we get a **deep red** layer (the red blood cells) at the bottom of the tube, a **clear yellow** layer (the plasma) at the top of the tube, and a sliver of **green** layer between them, which is called the buffy coat (all other cells not red blood cells or plasma). The plasma contains mostly water but also proteins such as **albumin** and **immunoglobulins** as well as the **clotting factors**. Blood separates like this when centrifuged, but it is not a meaningful way to view whole blood. This is the traditional approach, so we state it here. But the buffy coat has cells of immunity and cells of clotting; the plasma has proteins of immunity and proteins of clotting.

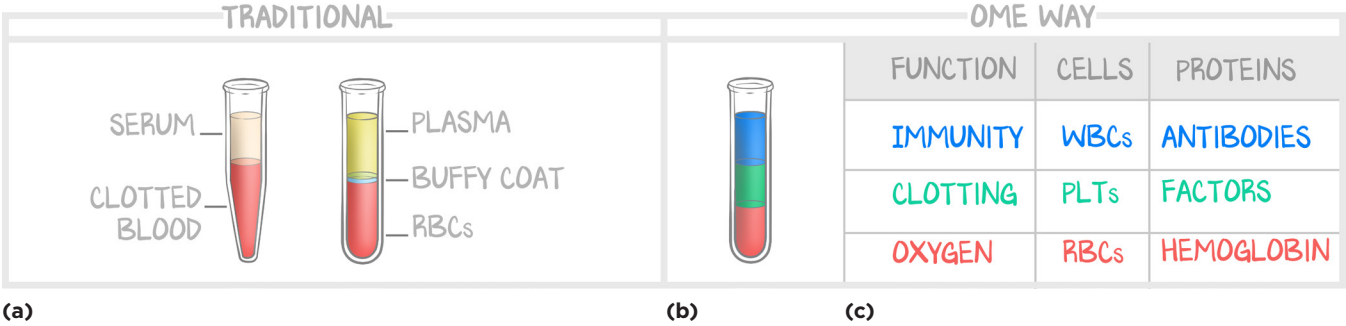

Figure 1.1: Whole Blood
(a) How whole blood is categorized by what happens in a centrifuge. (b) How whole blood is categorized when left to settle. (c) The OME way of categorizing the components of whole blood, the way that makes the most sense.

The better way to conceptualize the physiology of whole blood is not by how it separates in a centrifuge, but rather by separating out its functions. Conveniently, this is also how the complete blood count shorthand "stick method" is arranged. Whole blood consists of three functions—immunity, oxygen delivery, and clotting. Immunity is handled by the combination of cells of immunity, **white blood cells** (leukocytes), and proteins of immunity, **immunoglobulins.** Oxygen delivery is performed by the cells of oxygen delivery, **red blood cells** (erythrocytes), which also contain the protein of oxygen delivery, **hemoglobin**. Clotting is done by the combination of the cells of clotting, **platelets** (thrombocytes), and the proteins of clotting, the **clotting factors**.

There are **other molecules** that don't matter to blood—albumin, ions, and water. Albumin and total protein are lab tests that are obtained as part of liver function tests, and can provide information about the nutritional status of the patient or if there is an unusual amount of immunoglobulins around. Ions are evaluated on a basic metabolic prolife, which can give information both on the ions themselves and the overall water status of the patient. The other molecules do matter to clincal disease and to the patient. But we want you organizing hematology and the disorders of hematology according to the cells the bone marrow makes, how the complete blood count will deliver you information—WBCs, RBCs, Platelets.

The General series consists of this introductory lesson, a lesson on generic hematology laboratories, and a lesson on hematopoiesis. The remainder of the Hematology module is separated into WBCs (Proliferation), RBCs (Anemia), and clotting (Clotting).

White blood cells (leukocytes) can be deficient in number, as we saw in chemotherapy-related side effects and parvovirus B19 aplastic anemia, or as a side effect of TMP/SMX. However, the blood diseases of white cells, of white cells only, are going to be **proliferative disorders**, cancer. Diseases that result in deficiency of white blood cells will present with something other than the low white cells (such as anemia, thrombocytopenia, or both), which will direct you to consider a deficient bone marrow, where all blood cells come from. The WBC/Proliferation series does discuss disorders of too much erythropoiesis (red blood cell production) and of too much thrombopoiesis (thrombocyte, or platelet, production), but will mostly focus on cancers of the adaptive immune system, cancers of lymphocytes—leukemia, lymphoma, and plasma cell dyscrasias. The Immunology module had 16 lessons dedicated to white blood cells; you'll only find the pathologic conditions discussed here in Hematology.

Red blood cell disease often involves deficiency of red blood cells. **Erythrocytes** carry oxygen via hemoglobin. Their reason for existence is to ensure that the oxygen inspired into the lungs and passed to them across the alveolar membrane reaches the target tissues. The vascular system is designed to carry erythrocytes, and therefore oxygen, to the peripheral tissues. Without erythrocytes, the partial pressure of oxygen in the blood would be insufficient to sustain life. Oxygen dissolved in plasma is insufficient to sustain our tissues. Low red blood cells, or more importantly, low hemoglobin, is called anemia. In the Anemia series we will cover hemoglobin synthesis and function as well as disorders of heme synthesis, then move into iron physiology and anemia—an initial approach to anemia, then microcytic anemia, macrocytic anemia, and normocytic anemia.

Platelets are properly termed **thrombocytes**, and are responsible for **clotting**. But they cannot do it alone. Platelets and factors together form clots. Platelets form the initial response to endothelial injury, the platelet plug. The plug is flimsy and easily removed, but is stabilized by a fibrin clot via clotting factors. The clotting series explores the physiology and pathology of platelets, factors, and their interactions, and also covers clotting pharmacology, with an emphasis on stopping clots from forming.

Plasma is all noncellular components of blood. Plasma is 90% water and 10% everything else—mainly ions and proteins. The proteins are in the form of **albumin**, which provides oncotic pressure and transports drugs and other molecules (such as bilirubin); **immunoglobulins**, which fight infection; and **clotting factors**. Clotting factors are proteins. If blood is collected in a container without anticoagulants in it, the pooled blood will clot. What is left after clotting factors come out of the solution is **serum**. Serum is the same thing as plasma without clotting factors. Often, the words serum and plasma are used interchangeably, but in the context of hematology, they are quite different. In patients with low blood pressure but who also need to avoid sodium, aka cirrhotics, albumin can be used in lieu of normal saline to bolus fluids. Diluted albumin (5% albumin) is given for volume expansion. Concentrated (25% albumin) is given after large-volume paracentesis to prevent rebound and shock.

Shorthand

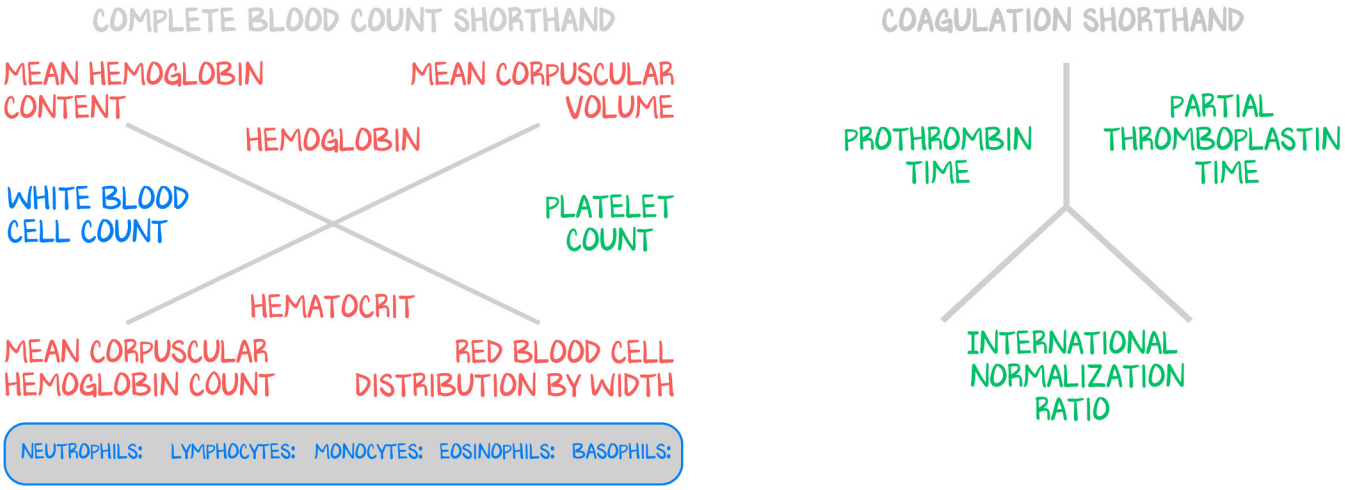

Figure 1.2: The CBC and Coagulation Panel Shorthand
This method of hand-recording laboratory values will become innate in clinicals. We get you used to it now. In addition, we can start showing you how the pieces are connected. The CBC measures hematopoiesis. The coags measure clotting factors. But the color coding is how you should group the labs conceptually.

We've color coded the module just as we have the CBC above.

Blue is for **white blood cells**. The number of white blood cells is reported as a two-digit number—a 10 would mean 10,000 white blood cells in the sample. The letters beneath the CBC sticks are the **differential**. Normally, there are between 4 and 12 WBCs, with a differential of **80% neutrophils**, **10% lymphocytes**, 5% monocytes, and an insignificant number of eosinophils and basophils. Too many leukocytes is called leukocytosis. Too few is called leukopenia.

Red is for **red blood cells**. Hemoglobin is a concentration (g/dL); hematocrit is a percentage (the percent of the height of a centrifuged test tube). Hematocrit is approximated by hemoglobin × 3. Pick one. Do not use or report both. We will use only hemoglobin. At the tips of the sticks, listed in red, are the **red blood cell indices**, values that will be explained in General #2: *Laboratory Interpretation*. The normal hemoglobin varies by sex, but 14–16 mg/dL is always normal. Too little hemoglobin is called **anemia**; too much is called **polycythemia**.

Green is for **clotting**. Notice the green things are for clotting, not a cell type. The cells involved in clotting, in the formation of a thrombus, are called thrombocytes, but are more often called **platelets**. The platelet count is listed on the right of the stick. The number of platelets is all that gets reported. As with leukocytes, thrombocytes are actually measured 120,000 to 400,000 as normal, but clinically we drop the "thousand" to save on syllables and eliminate superfluous words. The proteins that are involved in clotting are clotting factors. Factor clotting is measured with **coagulation studies**, the partial thromboplastin time (PTT), and the prothrombin time (PT). From here forward we will use only PT and PTT, and never spell the names out completely. The INR, at the base of the sticks, is based on the PT. The Mercedes-Benz stick is how you can track these values.

Blood Products

We can take blood out of people, separate the parts, and then give concentrated versions of the blood parts to other people, called a **transfusion**.

Packed red blood cells (PRBCs) restore the oxygen-carrying capacity of blood by delivering an increased number of red blood cells, those red blood cells having **hemoglobin**. While the red blood cell is the vehicle by which hemoglobin is delivered, you should start thinking in terms of hemoglobin only, and start ignoring how many red blood cells there are. We have the ability to monitor the hemoglobin, represented as a concentration in blood, irrespective of the number of red blood cells or their hemoglobin content. And since it is hemoglobin that transports the oxygen, the hemoglobin is what matters. Transfusions of PRBCs are indicated for a **hemoglobin < 7**, a patient who has **active hemorrhage** (and in whom you anticipate that the hemoglobin will fall below 7), or who is **symptomatic from anemia**. We will discuss for whom to choose transfusion in greater detail in Anemia #4: *Approach to Anemia*. **One unit** of PRBCs should increase the **hemoglobin by 1**.

If a patient is bleeding, the complete blood count assesses for platelet number, and coagulation studies evaluate for defects in the clotting cascade. Accept this generic statement for now, as it is covered in detail in General #2: *Laboratory Interpretation* and Clotting #1: *Hemostasis*. **Platelet transfusion** is indicated in platelet bleeding. Give platelets if a patient's platelets are < 10 (normal 120–400), < 50 and bleeding, or < 100 and planning a neurosurgical procedure. If the patient is suffering from a defective clotting cascade, as indicated by abnormal coagulation studies, there are several options. **Fresh frozen plasma** (FFP) is . . . plasma that is frozen. Plasma has all the clotting factors, albumin, water, etc. It is given to reverse factor bleeding. **Cryoprecipitate** was originally made to treat hemophiliacs, and has factor 8, factor 9, von Willebrand factor, and fibrinogen. "Cryo" is indicated when the fibrinogen is low, as found in disseminated intravascular coagulation, but rarely is used anymore because FFP contains fibrinogen as well, and hemophiliacs, who lack a specific clotting factor, can use factor concentrate. **Factor concentrate** contains the specific factor they need, and no other factors.

Leukocyte transfusion would be fatal. As discussed in Immunology, leukocytes identify antigens as foreign or self, with respect to the cell, not the organism it is currently in. Delivering a large quantity of white blood cells from another person would guarantee graft (the transfusion) vs. host (the recipient) disease. As discussed in Inflammation and Neoplasia, the only thing that can be done to increase the leukocyte count is colony-stimulating growth factor.

ABO Compatibility and Rh Status

There are two disease states that can arise from red blood cell antigens. The first, **ABO mismatch**, can be fatal. The second, **alloimmunization**, can result in future pregnancy loss. When a blood type is reported, the ABO phenotype (AB, A, B, or O) is suffixed with the Rh phenotype (+/–). As an example, B+ blood type means, "*expresses B antigen, does not express A antigen, and expresses the Rhesus antigen.*" So far in life, you have linked them together—the letter and plus or minus—but we are striving to break that link. ABO causes transfusion reactions and can be fatal. Rh mismatch causes future pregnancy loss. They are not at all interrelated except that they involve antibodies and are related to red blood cells.

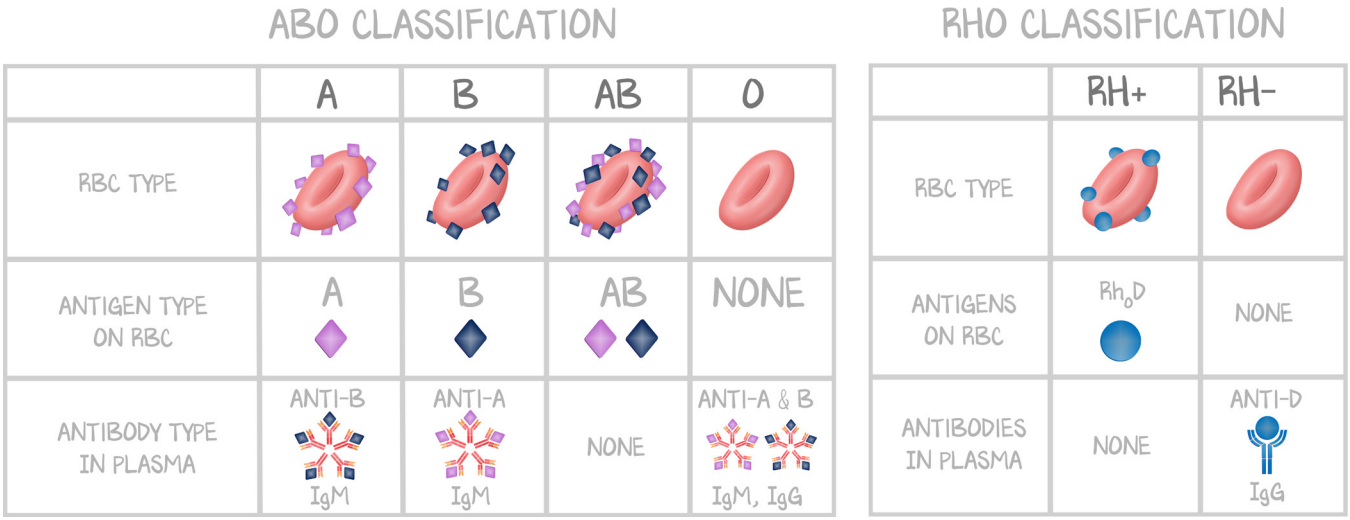

Figure 1.3: Antigens and Antibody Reactions
The ABO classification is dependent on two genes, the expression of two antigens. A person who expresses the antigen on their red blood cell will not have an antibody to the antigen and may receive blood with that antigen on the donor red blood cells. A person who does not express the antigen on their red blood cells will have an antibody to that antigen and will experience a hemolytic transfusion reaction if given blood with that antigen. A less severe form of immunization is seen in the RHO classification. If a mother does not express the Rh antigen, has a child that does, and their blood gets mixed, she will form antibodies that will target red blood cells of a future fetus who is also Rh antigen positive.

ABO mismatch is effectively a transplant rejection. We want you seeing O-type blood as having no antigen. Truthfully, it means "no A antigen and no B antigen are made," but it's easier if we keep it simple. A-type blood is blood that expresses only A antigen. B-type blood expresses only B antigen. AB-type blood expresses both antigens. The alleles for this gene are **codominant**—one copy as A and one copy as B make AB; one copy as A and one as O make A; two copies of A make A. When determining whether a transfusion can be made, we compare the **positive alleles only**. If the recipient has an Ag+, it indicates which antigens can be transfused—the positive antigens on the donor must be positive in the recipient. If the donor has Ag–, then it does not need to be considered. If the donor is antigen positive and the recipient not, the transfusion will be rejected. We are not sure how, but even in the absence of exposure to antigen previously, people who lack antigen **have antibody to the antigen they lack**. Even the first transfusion can be catastrophic—anaphylaxis kills. AB is the universal recipient; O is the universal donor. Use O– blood in emergencies when the blood type is unknown.

Rhesus antigen status as it relates to isoimmunization will be discussed in detail in Reproduction. What matters is if an Rh- mother gestates an Rh+ baby (because the father is Rh+), is unaware of the Rh+ status, and mixes blood during delivery or surgery. Her immune system will see the Rh+ antigen, recognize it as foreign, and mount a secondary immune response against it. This baby is fine, but mom develops IgG to Rh+ antigen. IgG can cross the placenta on the next Rh+ pregnancy and cause hemolytic disease of the newborn, or worse, fetal anemia. If mom knows she is Rh– and knows that dad is Rh+, **intravenous immunoglobulin** is administered at delivery to hide the Rh+ antigen from mom's immune system, preventing alloimmunization. The proper name for the rhesus antigen is $Rh_o(D)$, commonly "Rho-D," or Rho-D antigen, to which **anti-D IVIG** is given. Anti-D is anti-Rho-D antigen. There's nothing special about "anti-D."

Transfusion Reactions

While the names of the transfusion reactions are at the top of the table, the clinical syndrome you should look for is the last row of the table. Recognize anaphylaxis as IgE (Immune: Immunology #11: *Hypersensitivity Reactions*) and TRALI as donor antibody media.

ANAPHYLACTIC	HEMOLYTIC	FEBRILE	TRALI
Type I HSR	Type II HSR	Type II HSR	Type II HSR (sort of)
Preformed IgE primed on mast cells cross-links antigen	ABO mismatch or Unscreened preformed antibody against some antigen in blood	Donor white blood cells recognized as foreign and killed	Donor antibodies against neutrophils and pulmonary endothelial cells
Urticaria, hypotension, wheezing, shock	Fever, headache, flushing, and Hemolysis—jaundice, hemoglobinuria	Fever, headache, flushing, and NO hemolysis	ARDS after a transfusion, fever
IgA deficiency on second exposure is classic board fodder		Leukocyte-reduced blood avoids this; give leukoreduced to those who receive many transfusions	Roll of the dice. Could wash the PRBC, but risk so low not routinely done
Dying	Febrile and hemolysis	Febrile and not hemolysis	Lungs full of fluid

Table 1.1: Transfusion Reactions

Other Complications

Blood transfusion was once a major source of virus transmission. HIV, hepatitis C, and some other viruses of lower yield were transmitted through blood transfusion prior to 1983. Just as before we knew about ABO mismatch, we as a medical community did not put in fail-safes for virus transmission. Since 1983 in the United States, our screening processes have brought the chance of transmission via transfusion effectively to zero, but the consent forms still say that HIV can be contracted from blood transfusion. Patients, who are unaware of how unlikely it is, are made to decide whether they risk getting HIV or receive a life-saving transfusion (thanks, informed consent, serving only to induce anxiety in an already ill patient). Getting a blood transfusion OUTSIDE the United States, we cannot attest to. Takeaway—a patient may have HIV or Hep C because of a prior transfusion in their lifetime, but a patient will not contract HIV or Hep C from the blood transfusion you order for them today.

You also don't get a bacterial infection from a transfusion. It isn't possible for a bacterium to survive the processing and refrigerated storage of a unit of packed red blood cells. The bacterium doesn't go dormant, biding its time until it gets transfused into a new person. **Bacterial infections via transfusions are because of poor sterile technique while placing the IV before transfusion.** As with any venipuncture, proper sterilization technique is required. If you put a needle through skin without first wiping the skin, all that does is translocate bacteria from the skin into the vein.

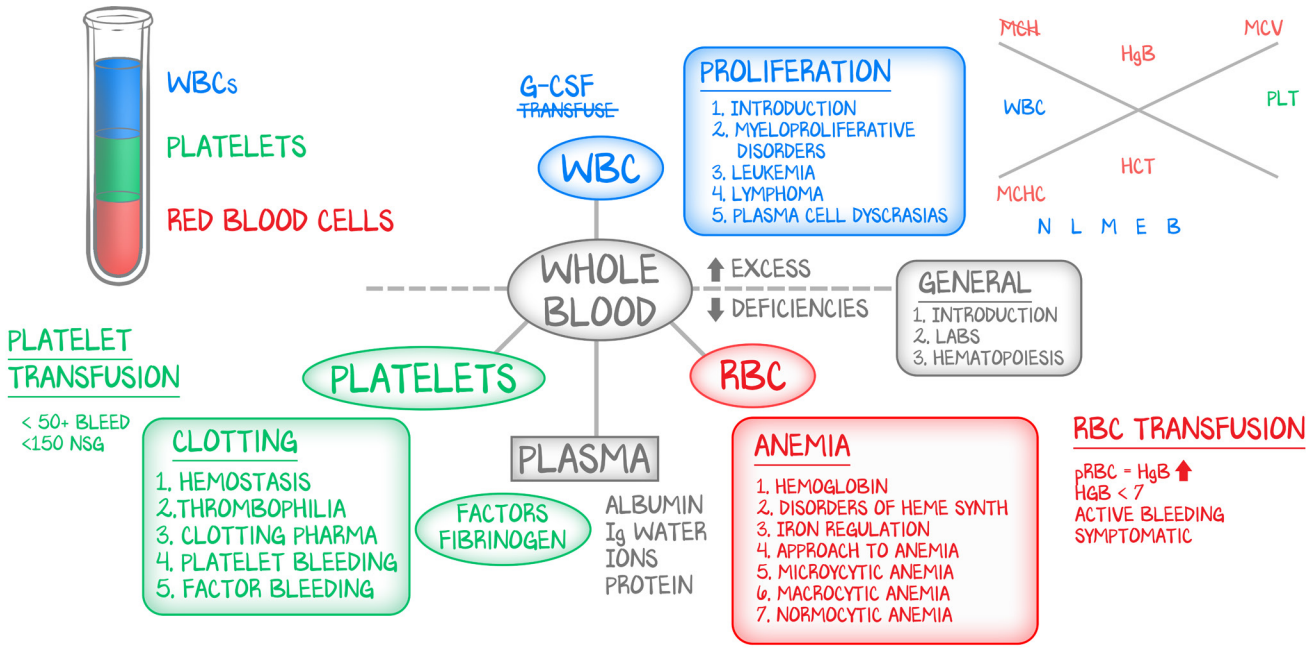

Figure 1.4: Layout for the Hematology/Oncology Module
Hematology/Oncology is organized the way a complete blood count shorthand is organized, based on the function of the cells and proteins rather than the layer they form whole blood is spun in a centrifuge. This illustration shows a color-coded map and a redrawing of the test tube to match the OME approach to whole blood. The General series orients you. The next expected series is Anemia, which covers red blood cells and the protein that allows red blood cells to perform their function, hemoglobin. The Clotting series discusses platelets and clotting factors as they cause arterial clots and venous thrombosis. You should then close with the Proliferation series, which covers malignancies of the bone marrow and secondary lymphoid tissue. Only nucleated cells can become malignant, so the majority of the series is on white blood cell malignancies.